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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/808,717

Applicant(s)

SAN ET AL.

Examiner

MALGORZATA A. WALICKA

Art Unit

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/CI/CD)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date 06/09/05

The amendment of Dec. 7, 2007 comprising amendment to table 2 and claims 27, 32 and 33 is acknowledged. Claims 27-33 are pending and under examination.

Detailed Action

Objections and rejections not repeated herein are withdrawn because applicant's arguments are found persuasive.

Rejections

35 USC section 112, first paragraph

Written description

Claim 31 is rejected for the reasons stated in the action of August 7, 2007 (last action). The rejection is repeated herein.

Certainly not any bacterium may be successfully transformed by *panK*, *pdh*, and *atf* genes to attain the goal of an increase in conversion of any alcohol to any ester as claimed in claim 31, simply because bacteria are very versatile in their metabolism. In case a cell produces a given alcohol, not described by the claim, the overexpression of the *atf* gene allows for an increase in production of its acetate unless the cellular metabolism does not prevent it. The claim is generic and does not identify an alcohol that is esterified into any ester. Neither does the disclosure. Disclosure teach production of isoamyl acetate in *E. coli* transformed with *atf* and having the isoamyl alcohol in the culture medium, because *E. coli* does not produce isoamyl alcohol. A skilled artisan realized that **any bacteria does not produces any alcohol, the conversion of which**

into any ester may be increased by an increase in CoA flux as recited by claim 27. Please note that claim 27 limits esters to acetate esters, in view of the fact that it recites using alcohol **acetyl** transferase gene for transformation. Acetate esters are not recited by claim 31. Addition of an alcohol as a substrate for production of the ester in the bacterium non-producing said alcohol is necessary, but may be toxic for the transformed host. In result of this toxicity production of the ester may be not possible. Thus, the alcohol recited in claim 31 may not be any alcohol but should be identified. In the case at hand Applicants have not described any bacterium producing any alcohol that after transformation with genes i), ii) and iii) of claim 27, i.e., after increasing CoA flux, increased conversion of the alcohol into ester. E. coli, the bacterium used by applicants, does not produce any alcohol (i.e., all alcohols) and their esters itself. In the instant application, to make E. coli a producent of isoamyl acetate applicants had to transform it with alcohol acetyl transferase gene and cultivate it in the presence of isoamyl alcohol. Thus, the definite alcohol was provided in the growth medium, and acetate ester was produced because E. coli was transformed with acetyl transferase. However, teaching conversion of isoamyl alcohol by acetyl transferase into isoamyl acetate does not teach conversion of any alcohol into any of its esters. All together, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention at the time the application was filed.

Response to applicants' traverse

Applicants' position presented in REMARKS at pages 6/16-8/16 is that the Examiners assertions are incorrect and the rejection is not properly supported, because

- 1) basic cell biochemistry conclusively establishes that no cell can exist in the absence of alcohol, for example, glycerol;
- 2) solventogenic bacteria produce significant amount of alcohols such as ethanol and butanol;
- 3) anyone of ordinary skill in the art knows how to keep ethanol within tolerance levels;
- 4) acetyl transferases have a very broad range of specificity and will work on many alcohols.

Applicants argument have been fully considered but are found not persuasive for the following reasons.

Regarding point 1) claim 31 is not directed to production of any ester of glycerol or glycerol acetate. The disclosure is silent about an increase in production of glycerol ester in bacterial cells transformed with the *panK*, *pdh*, and *atf* genes.

Regarding point 2) claim 31 is not directed to a method of an increase in production of alcohol ester in transformed solvatogenic bacteria. The specification does not disclose this as applicants' intention. Furthermore, claim 31 is not limited to the esters of ethanol and butanol. The fact that applicants did not mention in the disclosure any other alcohol than isoamyl alcohol is a proof that producing esters of other alcohols was not intended by applicants. Applicants produced isoamyl alcohol acetate using

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transformed *E. coli*. Please note that if glycerol, ethanol and butanol were entered to the claims now it would be a new matter.

Regarding point 3), claim 31 is not limited to an increase in production of esters of ethanol, wherein ethanol is in the culture medium.

Regarding point 4), although acetyl transferases may transfer acetyl group on many alcohols, claim 31 is not limited to acetic esters.

In conclusion, one having skills in the art is not convinced that applicants were in possession of the claimed invention at the time the application was filed.

Rejection for new matter

Claims 28, 32 and 33 remain rejected for new matter because of lack of written description of a bacterium cell having reduced activity of *ackA* or *pta*. Applicants teach they used *E. coli* YBS121 double mutant *ackA-pta* that has both genes inactivated. Neither the specification nor the claims as originally filed teach a bacterium cell having reduced activity of *ackA* gene or *pta* gene separately.

Response to applicants' traverse

Applicants' position presented in REMARKS at pages 8/16-9/16 is that

- 1) the specification specifically differentiates both enzymes:

"the A-CoA may be converted to acetyl phosphate by phosphotransacetylase (PTA), which in turn may be converted to acetate using acetate kinase (ACK)."⁵ Therefore, the specification states that

either enzyme may act on A-CoA, and each is in fact described as separate.”

2) “Examiner is apparently suggesting that because Applicants only used a ‘gift’ of a double mutant that the single mutants are not otherwise available. This is not true, as each individual mutant is already available. Thus, the single mutants are publicly available to one of ordinary skill in the art, including inventor Bennett. The prior art conclusively demonstrates that the single mutants were readily available and could be used to reduce activity of the acetate formation pathway. The ‘gift’ nature of the double mutant is irrelevant.”

Applicants argument have been fully considered but are found not persuasive for the following reasons.

Regarding point 1) Fig. 1 of the specification, teaches that acetyl CoA is converted to acetyl phosphate by phosphotransacetylase (PTA) and than acetyl phosphate is converted by acetate kinase (ACK) to acetate. ACK does not act on acetyl CoA and PTA does not act on acetylphosphate. That is why each “is in fact described as separate”. The activities of both enzymes are stated by their names. Only PTA acts on acetyl CoA. Inhibiting or inactivating any of the enzymes will increase the pull of acetyl CoA for producing acetic ester of alcohol as seen on Fig. 1. This biochemical pathway has nothing to do with the fact that applicants described and used in their

invention double mutant *ackA-pta*, and neither the specification nor the original claims suggest applicants' intention to use one or other mutant, i.e. *ackA or pta*.

Regarding point 2), although the single mutants are publicly available to one of ordinary skill in the art, including inventor Bennett, and the prior art conclusively demonstrates that the single mutants were readily available and could be used to reduce activity of the acetate formation pathway, applicants have not disclose the invention that uses such mutants. The disclosure is silent about using them. The language "*ackA or pta*" has been introduced to the claims together with the new set of claims 27-33 on Oct. 31, 2006. Furthermore, the language of applicants' argument "available" does not relate to the question of new matter but scope of enablement--not covered in this section of the Office Action.

Scope of enablement

Claim 31 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of production, and increasing the production of isoamyl acetate in *E. coli* transformed with genes (i), (ii) and (iii), and growing the transformants in the medium supplemented with pantothenic acid, does not provide a reasonable enablement for production of any ester of any alcohol.

The nature and breath of the claimed invention encompass production of any ester of any alcohol by any bacterium transformed with pantothenate kinase gene, pyruvate dehydrogenase gene, and alcohol acetyl transferase gene, wherein the transformed bacterium is cultivated in the presence of pantothenic acid.

While methods of producing esters by engineered bacteria are known in the art, and skills of the artisans well developed, no one is able to make any alcohol ester without indicating what alcohol takes part in esterification and which ester is to be produced. No bacteria produces any alcohol (i.e., all alcohols) as required by the claim, and the transformed bacteria that is to be used in the claimed invention overexpresses alcohol acetyltransferase, that may increase production of acetic ester and not other esters. Applicants intention was to engineer E. coli to make it a producer of acetic ester, however the claim is not limited to acetic ester.

Because the claim 31 does not state which alcohol is to be converted into which ester, one having skills in the art who would like to make the claimed invention is forced to experimentation that is not routine, and has a low probability of success. The disclosure lacks a guidance as to a suitable alcohol that is produced by the bacterium or which has to be supplemented to the culture medium thus enabling production of its ester. Providing for production of isoamyl acetate in E. coli grown in the presence of isoamyl alcohol does not provide an instruction or guidance how to make the claimed invention because the isoamyl alcohol does not identify any alcohol. Regarding the ester acetyl transferase, it cannot convert any alcohol into any ester, but only into acetic ester. The examiner concludes that without a further guidance on the part of applicants regarding the alcohol and its ester to be produced by the claimed method experimentation left to those in the art is improperly extensive and undue.

Response to applicant's traverse

Applicants' refers on page 10/16 of the REMARKS to the following examples of alcohols that are enabled by nature itself:

- 1) alcohol such as glycerol is present in all cells and in case of solvent producing bacteria alcohols such as ethanol or butanol are produced in the cell.

Furthermore, applicants' request the examiner provide

- 2) at least one example of an ATF that has a sole substrate and will not react with more than one alcohol.

Applicants argument have been fully considered but are found not persuasive for the following reasons. Regarding point 1), although by nature all cell produce glycerol and many bacteria produce ethanol or butanol, the disclosure does not contains the words "glycerol", "butanol" and "ethanol". Thus, production of these compounds is not enabled. The fact that applicants did not mention in the disclosure any other alcohol than isoamyl alcohol is a proof that production of esters of these alcohols was not intended by applicants and for that reasons is not enabled; see also the above response to traverse of rejection for lack of written description.

Regarding point 2), nowhere in her rejections the examiner stated that ATF has a sole substrate, because it is a common knowledge in the art that it has not. The issue here is not the sole substrate for acetyl transferase, but claiming any ester, not only the acetic ester for production of which ATF was used by applicants. Using ATF does not enable production of esters other than acetic esters. The examiner encloses a list of some esters of one other alcohol, i.e. ethanol, to support the fact that claim 31 is not enabled.

3.4. 35 USC 103

Claims 27-33 are rejected as being unpatentable over San et al. (Metabolic Engineering through Cofactor Manipulation and Its Effects on Metabolic Flux Redistribution in *Escherichia coli*, Metabolic Engineering, February 27, 2002, 4, 182-192, included in the Information Disclosure Statement), Song and Jackowski (Cloning, Sequencing and Expression of the Panthothenate Kinase (*coaA*) Gene of *E. coli*, J. Bacteriol, Oct. 1992, 174, 6411-6417; copy enclosed with the action of 08/07/07); Russell and Guest al. 1992 (Overproduction of the pyruvate dehydrogenase multicomplex of *Escherichia coli* and site-directed substitutions in the E1p and E2p subunits, Biochem. J. 287, 611-619 copy enclosed); Voet et al. (Biochemistry, second Edition, 1995, John Wiley & Sons, Inc, pp. 543-548, mailed to applicants with the action of 1/29/07); Rock C. et al., (Panthothenate Kinase Regulation of the Intracellular Concentration of Coenzyme A, J. Biol. Chem, 2000, 275, 1377-1387, mailed to the applicants with the action of 06/30/06), as well as over Yang et al. (Effect of Inactivation of *nuo* and *ackA-pta* on Redistribution of Metabolic Fluxes in *Escherichia coli*, Biotech. Bioeng. 1999, 65, 291-297, mailed to applicants with the previous action).

Claim 27-30 are directed to a method of increasing CoA flux in a bacterial cell comprising transforming the cell with pantothenate kinase gene, pyruvate dehydrogenase gene, and alcohol acetyl transferase gene, and in case of claim 29 in addition by reducing activity of *ackA* or *pta* or *ackA-pta* genes; wherein the transformed cell is cultivated in the presence of pantothenic acid and isoamyl alcohol when

necessary. The claims are directed to a method of manipulating the metabolism of the bacteria by an increase in carbon flux through the acetyl-CoA node. Claim 31 is directed to a method of producing any ester of any alcohol including acetate ester, and claim 32-33 are directed to production of isoamyl acetate.

San et al. 2002, in Fig. 6a teach that CoA is synthesized in a series of reactions which start with phosphorylation of pantothenic acid by pantothenate kinase (panK).

Song and Jackowski disclose the pantothenate kinase (*coaA*) gene of *E. coli*, and its recombinant multicopy expression for production of CoA in *E. coli*. Song and Jackowski 1992 teach that the regulation of pantothenate kinase step is the most important determinant of the CoA synthesis rate in *E. coli* (bacterial cell) and that pantothenate kinase is feedback inhibited by CoA; see introduction line 13.

Rock et al. 2000 teach, page 1377, right column line 4:

"PanK is the rate-controlling enzyme in CoA biosynthesis in *Escherichia coli* (1). *E. coli* is capable of de novo pantothenate biosynthesis, and additionally a sodium-dependent permease actively transports exogenous pantothenate into the cell (7-9). Metabolic labeling experiments established that the utilization [emphasis added], rather than the supply of pantothenate, controls the level of CoA (10). "

Along these lines they demonstrate, page 1380 right column,

"cells overexpressing mPanK1 β [mammalian PanK] did not accumulate pantothenate but readily metabolized it (Fig. 5B and Fig. 6). The total uptake of

D-[1-¹⁴C]pantothenate also increased by about 4-fold in response to overexpression of mPanK1 (Fig. 6)."

The authors conclude that the overexpression of pantothenate kinase influences the uptake and metabolism of pantothenate and regulate the cellular CoA content.

San et al. teach in Fig. 6b that CoA and pyruvate are used for synthesis of acetyl-CoA by pyruvate formate lyase under anaerobic conditions. Under aerobic condition pyruvate is used by pyruvate dehydrogenase in conversion of CoA in acetyl-CoA, see for example, Russell and Guest al., the introduction to their article of 1992. The quoted biochemistry handbook teaches on page 547 that pyruvate dehydrogenase is inhibited by acetyl-CoA.

Russel at al. also discover **plasmid pGS367** comprising pyruvate dehydrogenase gene of E. coli. This very plasmid was used by Applicants to overexpress pyruvate dehydrogenase in E. coli; see page 8 [41] of the specification where one reads "plasmid pGS3670 (Pyruvate dehydrogenase expression plasmid) was obtained from Dr J. R. Guest [Dr. Guest is an author on the article by Russell et al.]".

San et al. 2002 in Fig 6B, teach that alcohol acetyl transferase (AAT, in the instant application ATF) uses acetyl-CoA as a source of acetyl in synthesis of acetate ester from an alcohol. Thus, San et al, 2002, teach the flux of CoA from its synthesis starting with pantothenate kinase, through pyruvate dehydrogenase to acetyl-CoA and San et al 2002 teach further the transfer of acetyl group from acetyl-CoA to alcohol by alcohol acetyl transferase.

Yang et al 1999 teach in Fig. 1 that phosphoacetyltransferase (*pta*) and further acetate kinase (*ackA*) use acetyl-CoA for phosphorylation and production of acetate. Thus, these enzymes compete in acetyl Co-A node with alcohol acetyl transferase for acetyl group of acetyl-CoA. Cutting out *pta* –*ackA* pathway would divert acetyl-CoA to its node. Yang et al used E. coli mutant having inactivated *pta* –*ackA* that produced acetyl-CoA but did not produced acetate; see Table IV, page 295.

San et al. 2002 teach transformation of E. coli with a plasmid encoding ATF2 and cultivating transformants in a medium supplemented with 10 mM isoamyl alcohol. Because E. coli itself does not synthesize isoamyl alcohol, thus isoamyl acetate would be only formed when isoamyl alcohol is added externally; see the paragraph bridging page 190 and 191.

Taking into account the above described teachings one having skills in the art, who would like to increase CoA flux in a E. coli (bacterial cell) or efficiently produce isoamyl acetate in bacterial cell would transform it with a multicopy *panK* plasmid and grow it in the presence of extracellular pantothenate. Furthermore one having skills in the art would transform E. coli with *pdH* gene to increase production of acetyl-CoA. And finally, one having skills in the art would transform bacterial cell with ATF and grow it in the presence of isoamyl alcohol to obtain isoamyl alcohol acetate. Transformation with *panK* would increase concentration of CoA in the cell in the first place. Transformation of the cell with *pdH* would increase the use of CoA for synthesis of acetyl-CoA. Thus, PANK would not be inhibited by CoA, which would fuel further synthesis of CoA by PANK. Use of acetyl-CoA by ATF would release feedback inhibition of PDH by Acetyl-

CoA which would promote its further synthesis from pyruvate and CoA, and in this situation also further synthesis of CoA. Finally, using cells that have inactivated *pta* – *ackA* would increase the amount of acetyl–Co in its node increasing the concentration of acetyl available for ATF in acetate ester synthesis. Thus, based on the knowledge of metabolic pathways from pantothenate and CoA to ester at the time of invention, as presented in the quoted sources, and skills in the art at the time of invention, the skilled artisan who would like to increase the carbon flux from CoA through Acetyl–CoA to esters would overexpress of *panK*, *pdh* and *atf* and would provide exogenous pantothenate to provide the proper substrate concentration for the increase of PANK concentration resulting from its overexpression.

Probability of success in transformation with the genes is very high as evidenced by Song and Jackowski for *panK*, and by San et al for *atf* and Russel et al. for *pdh*, as well as, because at the time if invention transformation of bacterial cell with endogenous or exogenous genes was a routine practice. All claimed elements were known in the prior art and one of ordinary skills in the art could have combined the elements as claimed with no change in their respective functions, and the combination would yielded predictable results to one of ordinary skill in the art at the time of the invention. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

Applicants' attention is turned to the fact that the *prima facie* obviousness is supported by Dr. Bennett's Declaration filed June 29, 2007 in which he writes, presenting the states of art at the time of invention "Overexpression of pantothenate

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kinase will increase coenzyme A production in **all** characterized bacterial species" and further, "Thus, expression of pantothenate kinase, pyruvate dehydrogenase, and alcohol acetyl transferase described in claims 27-33 will increase CoA flux to secondary metabolites in all bacteria."

In conclusion, the state of art at the time of invention makes the invention obvious.

Response to Applicants arguments

Applicants position regarding 103 rejection made in the previous action is presented at pages 11/16-16/16 of REMARKS. Applicants argue that *prima facie* case is not made because:

- 1) the examiner does not provide a reference teaching "recombinant *pdh* gene";
- 2) Song et al had to supplement the cultures of *E. coli* with pantothenate because they used a mutant with abolished endogenous pantothenate production;
- 3) Examiner cites Vadali et al (Metab. Eng. 6:113-9 (2004), that is not a prior art but applicants' own work, thus the cited art does not show recombinant *pank* cells require supplementation with pantothenate and supplementation requirement is unexpected;
- 4) quoting inventors own Declaration is an impermissible hindsight and carbon flux increase is unexpected.

Regarding point 1), the recombinant *pdh* gene applicants used for generating *E.*

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coli with increased CoA was contained in pGS367; see Table 2 of the specification. The plasmid was a gift from Dr. Guest who constructed it for overexpression of *pdh* gene in *E. coli* at least 10 years before the invention; see the above quoted article by Russell et al., 1992.

Regarding point 2) and 3), indeed, the examiner has not noticed that the *E. coli* mutants used by Song did not produced pantothenate. However, other experiments, performed or referred to by Rock et al., as presented in the body of rejection above, provide an evidence that overexpressing *panK* requires and increase in the concentration of its substrate, i.e. pantothenate. The examiner quoted Vadali et al., 2004 to illustrate the fact that possibility of insufficient supply of pantothenate in case of overexpressed *PANK* was real from a biochemical point of view and because others have shown that. In the Vadali's section **Results and Discussion** *Characterization of DH10B (pUC19) and DHN(pRV380) in aerobic shake fasks*, page 135 presents results for *E. coli* transformed with a plasmids comprising **high copy number of *E. coli panK* genes**. This overexpression, however, did not lead to an increase in the intracellular CoA/acetyl-CoA levels. Although the authors noted that not transformed *E. coli* contain excess amount of pantothenate acid and secrets it to the extracellular medium (right column of page 135, second line of the second paragraph), the authors also concluded (further in the same paragraph), as a skilled artisan would,

"With the **overexpression of the pantothenate kinase, the availability of pantothenic acid might be rate limiting**. To test the requirement of concentration of pantothenic acid, a doseage study

was performed... The results are shown in Fig.1. The results suggest that ~50 uM of pantothenic acid concentration in the cell culture medium is sufficient **to saturate the enzymatic activity of overexpressed pantothenate kinase** resulting in highest In response to point 20 and 30 intracellular acetyl-CoA levels [emphasis added by the examiner]."

In response to points 2) and 3) Applicants' attention is turned to the fact that if *E. coli* were transformed with one or two additional copies of *panK*, the supplementation would have been probably not necessary. In summary, at the time of filing, it was obvious that bacteria comprising many copies of *panK* gene would require supplementation with pantothenic acid to **saturate the enzymatic activity of overexpressed pantothenate kinase** and thus increasing the CoA flux through the acetyl CoA node. In conclusion, the applicants experiments yielded results that were predictable to Applicants themselves and to one having skills in the art. **Thus the supplementation has no feature of novelty.**

Regarding point 4, as presented above, and in Dr. Bennett's Declaration, the carbon flux from CoA to esters was well known at the time of invention. Dr. Bennett's declaration is not related to particularities of the disclosure. The Declaration is a general statement of the state of art at the time of invention. Quoting this Declaration as a support in 103 rejection is not an "impermissible hindsight".

In summary, Applicants describe the method of increasing the carbon flux by overexpressing genes of enzymes participating in the flux and supplying the substrat of the controlling reaction that is phosphorylation of pantothenate by PANK. The

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invention would have been obvious because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. In the instant case this has led to the anticipated success. The method is not of innovation but of ordinary skill and common sense.

The rejection for obviousness is not withdrawn.

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Malgorzata A. Walicka, Ph.D.

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Patent Examiner

/Yong D Pak/

Primary Examiner, Art Unit 1652